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(54) Title: METHOD FOR PREPARING ω-AMINOALKANOIC ACID DERIVATIVES FROM CYCLOALKANONES

(57) Abstract

A convenient synthetic route to ω-aminoalkanoic acids, *N*-Boc protected ω-aminoalkanoic acids and Boc-amino acid coupled ω-aminoalkanoic acids is disclosed. The method provides high purity compounds that generally do not require further purification.

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METHOD FOR PREPARING ω -AMINOALKANOIC ACID DERIVATIVES FROM CYCLOALKANONES

FIELD OF THE INVENTION

The present invention relates to a method for the preparation of ω-aminoalkanoic acids, *N*-Boc protected ω-aminoalkanoic acids, and Boc-amino acid coupled ω-aminoalkanoic acids.

BACKGROUND OF THE INVENTION

ω - Aminoalkanoic acids have a wide variety of applications. One such use is as spacer molecules in solid phase peptide synthesis (SPPS). These spacer molecules serve to distance the growing peptide chains from the solid resin support allowing the supported biopolymers to be more accessible for subsequent chemical reactions. *J. Org. Chem., 41*, page 1350, (1976). Incorporation of such spacers can be important in the preparation of combinatorial libraries wherein large enzymes or antibodies are frequently used to assess the *in-vitro* activities of the pendant peptides. Minimization of restrictions exerted by the resin allows a more effective interaction between the protein and peptide, *Immunomethods, 1*, page 11, (1992).

For example, substituted 6-aminocaproic acid derivatives have been used to induce and maintain conformational rigidity in peptide

fragments. The resulting cyclic peptidomimetic compounds have β-turn structures. *J. Am. Chem., 117*, page 5169, (1995).

The ω -aminoalkanoic acids are also used in the covalent modification of antigenic peptides with lipophilic moieties such as aminohexadecanoic acid or lauric acid to enhance immunogenicity. For example, a laurylpetide adjuvant can be coupled to a 16 amino acid peptide from the V3 loop of the third hypervariable domain of the HIV-1 to envelope glycoprotein gp 120. This adjuvant-linked peptide stimulated elevated immune responses when compared to the peptide alone. *J. Med. Chem., 38*, page 459, (1995).

The ω-aminoalkanoic acids can also serve as useful synthetic "handles" for these adjuvants since these acids contain both amino and carboxylic termini which can be further derivatized.

Because of the many uses for ω-aminoalkanoic acids, there is a need in the art for a simple, inexpensive route to prepare these ω-aminoalkanoic acids and their derivatives. A number of methods for the preparations of ω-aminoalkanoic acids have been reported. The amine group on the ω-aminoalkanoic acids can be introduced by first converting a ketone to an oxime using hydroxylamine sulfonic acid. The ω-hydroxyimino acids formed are then reduced using Raney nickel to provide ω-aminoalkanoic acids. (French Patent 1,349,281, January 7, 1964). The preparation of ω-aminoalkanoic acids by reduction of an organic acid with a terminal nitrile to an amine, with lithium aluminum hydride, has also been reported. The nitriles were prepared by conversion of an acid having a terminal group such as a halogen to a nitrile group. *Chem. Tech., 8*, page 187, (1956). Other methods require formation of an anhydride from an organic diacid followed by opening the anhydride with an azide. The intermediate compound was rearranged via a Schmidt rearrangement at an elevated temperature (50-60°). *Chem & Pharm. Bull., 7*, page 99, (1959). Cyclic anhydrides have been opened with concentrated ammonium hydroxide followed by warming to about 50° and addition of sodium hydroxide to provide the corresponding half amide. The half-amide can be converted to the corresponding ω -

aminoalkanoic acid by Hofmann rearrangement using aqueous base and bromine. *Chem. Ber., 89*, page 117, (1956).

Boc protected ω-aminoalkanoic acids have been prepared from lactams that have been previously acylated with a *t*-butyloxycarbonyl acylating agent. The *N*-acylated lactam product can be treated with a base in aqueous tetrahydrofuran to provide the *N*-butoxycarbonyl ω-aminoalkanoic acids by hydrolysis. However, chromatographic purification of the *N*-butoxycarbonyl lactams is usually required. *J. Org. Chem., 48*, page 2424, (1983).

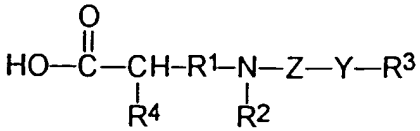
Aubé *et al.* recently reported the synthesis Boc protected peptides of methyl substituted 6-aminohexanoic acid. A lactam was prepared and opened with hydrochloric acid solution. The ring opened lactam can be coupled to the peptide. However, this procedure required protection of the carboxyl terminus of the 6-aminohexanoic acids as a methyl esters before coupling with the peptide. *J. Med. Chem., 117*, page 5169, (1995).

Each of the preceding methods have difficulties such as low yields, the need for purification, expensive reagents and/or scale-up problems.

SUMMARY OF THE INVENTION

A convenient synthetic route to acylated ω-aminoalkanoic acids *N*-Boc protected ω-aminoalkanoic acids or Boc-amino acid coupled ω-aminoalkanoic acids is disclosed. The method of the invention provides high purity compounds that generally do not require further purification.

The invention provides a method for the preparation of a compound having the formula:



wherein

Y is carbonyl, C_1-C_4 alkyl carbonyl, oxycarbonyl, C_1-C_4 alkyl oxycarbonyl, or SO_2;

Z is a bond, an amino acid residue, a peptide residue, or a poly amino acid residue;

R^1 is C_1-C_{24} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

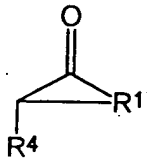
R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, cycloalkyl, heterocyclic, aryl, or heteroaryl; and

R^3 is C_1-C_7 alkyl, C_3-C_{10} cycloalkyl, phenyl, aryl, thienyl, pyrrolo, or pyridyl, where R^3 is optionally substituted by one or more C_1-C_5 alkyl, C_2-C_4 alkenyl group, C_1-C_5 alkoxy, C_1-C_5 alkylamino, di-C_1-C_5 alkylamino halogen, OH, NO_2, NH_2, SO_2, COOH, or SO_3H;

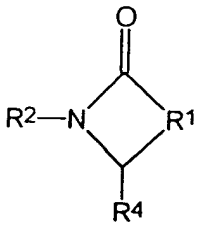
R^4 is C_1-C_7 alkyl, C_3-C_{10} cycloalkyl, aryl, thienyl, pyrrolo, or pyridyl, where R^4 is optionally substituted by one or more C_1-C_5 alkyl group, C_2-C_4 alkenyl group, F, Cl, OH, SO_2, COOH, or SO_3H.

The method comprises:

(a) reacting a cycloalkanone compound having the formula:



with formic acid and hydroxylamine-*O*-sulfonic acid to provide a lactam having the formula:



(b) reacting the lactam with an aqueous base to form an amine salt; and

(c) acylating the amine salt with a compound having the formula

$$R^3 - Y - Z - X$$

wherein R^1, R^2, R^3, R^4, Z and Y are as defined above and X is a leaving group.

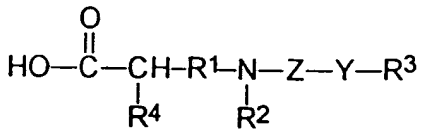
Advantages of the present invention include the use of easy to prepare, and/or inexpensive raw materials. The method of the present invention is cost effective, simple to perform, and amenable to industrial scale up for commercial production.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a convenient synthetic route to ω-aminoalkanoic acids,acylated ω-aminoalkanoic acids *N*-Boc protected ω-aminoalkanoic acids and Boc-amino acid coupled ω-aminoalkanoic acids. The method described herein provides syntheses of ω-aminoalkanoic acid analogs that generally do not require further purification or protection of the carboxyl function. These compounds are prepared with less handling. In addition, by avoiding hydrogenation, azide or bromine related rearrangements, the syntheses are very readily amenable to scale-up.

The compounds have been prepared amounts up to 1 kg with high purity. Consequently, these compounds are suitable for solution or solid phase peptide synthesis using BOC chemistry. Homologues with variable chain length maybe prepared by using different cycloalkanones.

The method of the invention provides a preparation of compounds having the formula:



wherein

Y is carbonyl, C_1-C_4 alkyl carbonyl, oxycarbonyl, C_1-C_4 alkyl oxycarbonyl, or SO_2;

Z is a bond, an amino acid residue, a peptide residue, or a poly amino acid residue;

R^1 is C_1-C_{24} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

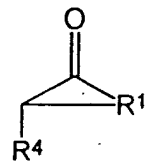
R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, cycloalkyl, heterocyclic, aryl, or heteroaryl; and

R^3 is C_1-C_7 alkyl, C_1-C_7 alkoxy, C_3-C_{10} cycloalkyl, phenyl, aryl, thienyl, pyrrolo, or pyridyl, where R^3 is optionally substituted by one or more C_1-C_5 alkyl, C_2-C_4 alkenyl group, C_1-C_5 alkoxy, C_1-C_5 alkylamino, di-C_1-C_5 alkylamino halogen, OH, NO_2, NH_2, SO_2, COOH, or SO_3H;

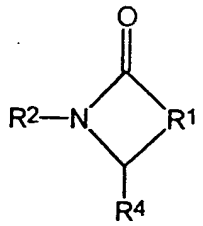
R^4 is C_1-C_7 alkyl, C_3-C_{10} cycloalkyl, phenyl, aryl, thienyl, pyrrolo, or pyridyl, where R^4 is optionally substituted by one or more C_1-C_5 alkyl group, C_2-C_4 alkenyl group,C_1-C_5 alkoxy, C_1-C_5 alkyl-amino, di-C_1-C_5 alkylamino halogen, OH, NO_2, NH_2, SO_2, COOH, or SO_3H.

The method comprises:

(a) reacting a cycloalkanone compound having the formula:



with formic acid and hydroxylamine-*O*-sulfonic acid to provide a lactam having the formula:



(b) reacting the lactam with an aqueous base to form an amine salt; and

(c) acylating the amine salt with a compound having the formula

$$R^3 - Y - Z - X$$

wherein R^1, R^2, R^3, R^4, Z, and Y are as defined above and X is a leaving group.

In a preferred embodiment the Y is oxycarbonyl, and Z is a bond or an amino acid residue; R^1 is alkyl having from 5 to 9 carbon atoms; R^2 and R^4 are hydrogen; and R^3 is C_1-C_4 alkyl or phenyl. The most preferred R^3 is *tert*-butyl.

Compounds useful for acylating or sulfonating the amine salts of the invention have the formula

$$R^3 - Y - Z - X$$

wherein:

R^3 is C_1-C_7 alkyl, C_3-C_{10} cycloalkyl, phenyl, aryl, thienyl, pyrrolo, or pyridyl, where R^3 is optionally substituted by one or more C_1-C_5 alkyl, C_2-C_4 alkenyl group, C_1-C_5 alkoxy, C_1-C_5 alkylamino, di-C_1-C_5 alkylamino halogen, OH, NO_2, NH_2, SO_2, COOH, or SO_3H;

Y is carbonyl, alkyl carbonyl, araalkyl carbonyl, oxycarbonyl, alkyl oxycarbonyl, araalkyl oxycarbonyl, or SO_2; Z is an amino acid residue, a peptide residue, or a poly amino acid residue and X is a leaving group.

Typical leaving groups include, but are not limited to, halogens such as, for example, chlorine, bromine, and iodine. Additionally, the corresponding anhydrides can be used as acylating agents.

A preferred compound for acylating the amine salt is a compound having the formula

$$(CH_3)_3C - O - CO - Z - X$$

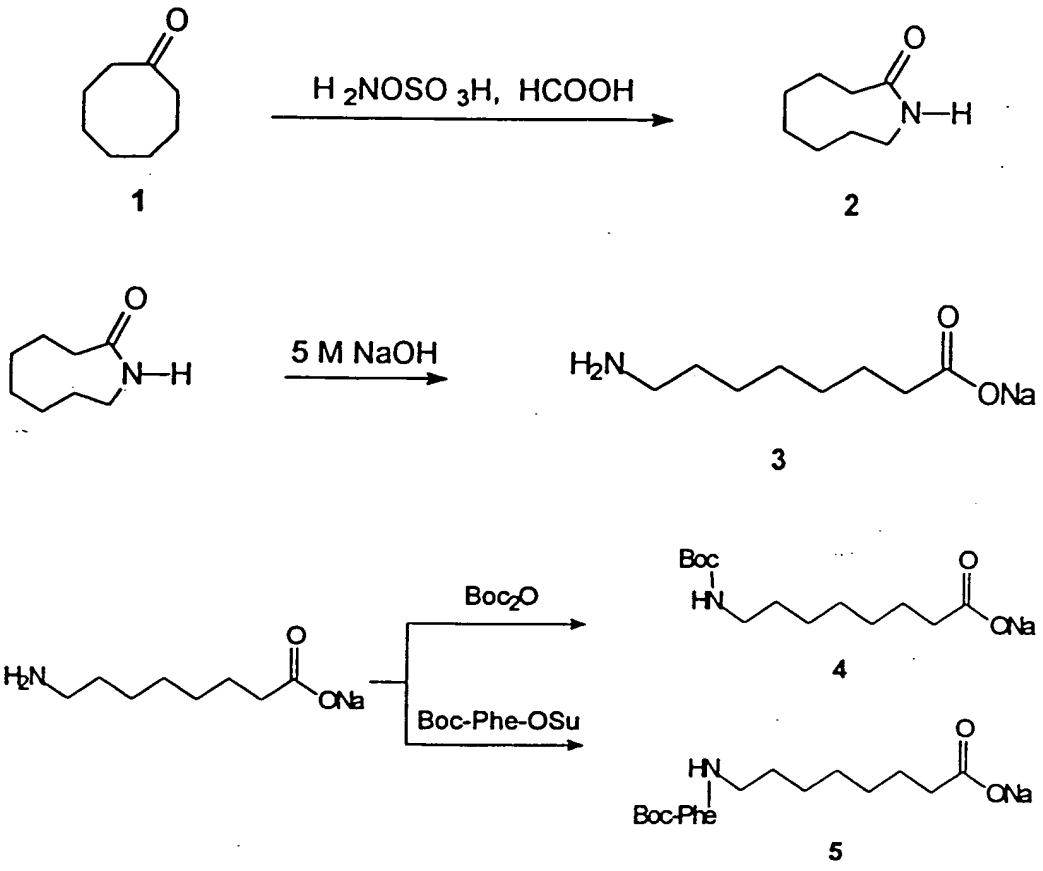
where Z is a bond or an amino acid residue, X is a leaving group. Examples of preferred acylating compounds include compounds such as, for example, $((CH_3)_3COCO)_2O$ and Boc protected amino acid succinate esters. A preferred acylating group where Z is an amino acid residue is a Boc protected amino acid-*O*-succinate ester such as, for example, Boc-phenyl alanyl-O-succinate ester.

An amino acid residue is an amino acid which has a hydrogen atom removed from either or both the amine or acid end of the molecule. An amino acid is any carboxylic acid having at least one free amine group and includes naturally occurring and synthetic amino acids. The invention includes amino acid residues where the amino acid residue is a single amino acid, a peptide, and a poly amino acid

A poly amino acid residue is a poly amino acid which has a hydrogen atom removed from either or both of an amine or acid group of the molecule. Poly amino acids are either peptides or two or more amino acids linked by a bond formed by other groups which can be linked, e.g. an ester, anhydride, or an anhydride linkage.

A peptide residue is an peptide which has a hydrogen atom removed from either or both the amine or acid end of the molecule. Peptides are two or more amino acids joined by a peptide bond. Peptides can vary in length from dipeptides with two amino acids to poly peptides with several hundred amino acids. See Chambers Biological Dictionary, editor Peter M. B. Walker, Cambridge, England: Chambers Cambridge, 1989, page 215.

The method of the invention is illustrated by the following scheme:



The cyclooctanone, Compound **1**, is treated with formic acid and hydroxylamine-*O*-sulfonic acid to provide the lactam, Compound **2**. The lactam is then hydrolyzed with an aqueous base, such as sodium hydroxide, to provide the amine salt, Compound **3**.

The Boc protected 8-amino caprylic acid, Compound **4** was prepared from a solution of the amine salt, **5**, by the addition of di-t-butyl-dicarbonate. A 63% yield of 8-(t-butoxycarbonylamino)caprylic acid, **4**, was isolated based on the lactam, **2**.

Attempts to acylate the free amine of 8-amino caprylic acid, with an O-succinic (-OSu) ester of a Boc-amino acid failed. The major product was the parent Boc-amino acid resulting from hydrolysis of the

O-succinic ester. When the using the amine salt for the acylation with the Boc-Phe-OSu this problem was overcome. The amount of hydrolysis of the O-succinic ester was reduced and a 43% yield (over two steps) of the desired (N-t-butoxycarbonylphenylalanyl)-8-amino caprylic acid, Compound 5 was obtained.

Thus, the *N*-Boc protected or Boc-amino acid coupled ω-amino-alkanoic acids were readily prepared using the method of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate the invention without limitation. All parts are given by weight unless otherwise indicated.

Example 1: Synthesis of 2-Azacyclononanone (2)

A 5 L three-neck round bottom flask was fitted with a heating mantle, an overhead mechanical stirrer, an addition funnel, and a thermometer. The reaction was performed under an argon atmosphere. Hydroxylamine-*O*-sulfonic acid (196.7 g, 1.74 moles, 1.10 equiv.) and formic acid (1 L) were charged into the round bottom flask and stirred to form a white slurry. A solution of cyclooctanone (200.0 g 1.58 moles, 1.0 equiv.) in formic acid (600 mL) was added dropwise to the white slurry via the addition funnel. After the addition, the addition funnel was replaced by a reflux condenser, and the reaction was heated to reflux (internal temperature about 105°C) for 1 hour to give a brown solution. After the solution was cooled to room temperature, it was poured into a mixture of saturated aqueous ammonium chloride (1.5 L) and water (1.5 L). The aqueous mixture was extracted with chloroform (3 x 1200 mL). The combined chloroform layers were transferred into a beaker, and saturated sodium bicarbonate (2 L) was added slowly. The chloroform layer was then separated, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to afford a brown oil. The oil was placed in a 500 mL round bottom flask with a magnetic stirrer. The round bottom flask was placed in a silicon oil bath and

was fitted with a short path vacuum distillation head equipped with a thermometer. A Cow-type receiver was connected to three 250 mL flasks. 2-Azacyclononanone (145 g, 65%, mp 64-69°C) was obtained by vacuum distillation (fraction with head temperature range from 80 to 120°C at pressures between 3.0 and 3.4 mmHg).

Example 2: Sodium 8-Aminocaprylate (3)

A 5 L three-neck round bottom flask was fitted with a heating mantle, an overhead mechanical stirrer, a reflux condenser, and a thermometer. A suspension of 2-azacyclononanone (83 g, 0.59 moles, 1.0 equiv.) in 5 M aqueous sodium hydroxide (650 mL, 3.23 moles, 5.5 equiv.) was charged into the round bottom flask. The mixture was heated to reflux (internal temperature about 110°C) for 4 hours to yield a clear yellow solution. The heating mantle and reflux condenser were removed. After the solution cooled to room temperature, it was diluted with water (650 mL) and cooled further in an ice bath.

Example 3: 8-(*tert*-Butoxycarbonylamino)caprylic acid (4).

To a 250 mL three-neck round bottom flask equipped with a magnetic stirrer and an addition funnel, was added a solution of sodium 8-aminocaprylate (0.45 mmol mL^{-1}, 22.5 mmol, 50 mL). The solution was cooled in an ice-bath. Di-*tert*-butyl dicarbonate (24.75 mmol, 5.40 g, 1.1 equiv) was dissolved in dioxane (50 mL), charged to the addition funnel and added dropwise over 15 min. The mixture was stirred in the ice-bath for 15 min and at ambient temperature for 1 h. The dioxane was evaporated under vacuum, ethyl acetate (30 mL) was added and the heterogeneous solution was cooled in an ice-bath. The solution was acidified with 0.5 M sulfuric acid to pH 2. The ethyl acetate was separated and the aqueous layer was further extracted with 2 x 30 mL ethyl acetate. The combined organic layers were washed with water (2 x 30 mL), dried and evaporated. The residue was suspended in hot hexanes (30 mL), followed by dropwise addition of ethyl acetate until a homogenous solution was obtained. The solution was

cooled at -5°C for 4h. A white solid formed and was collected by filtration to afford 8-(*tert*-butoxycarbonylamino)caprylic acid (4) (3.67 g, 63%).

Properties are listed below.

Mp 54-55°C;

IR(KBr); 3362, 2947, 1690, 1520, 1321, 940 cm^{-1}.

^1H NMR (DMSO-d_6)δ: 11.93 (br s, 1H), 8.72 (br s, 1H) 2.87 (q,J=6.54, 12.86 Hz, 2H), 2.19 (t,J=7.33 Hz, 2H), 1.47 (m, 2H), 1.36 (br s, 11H), 1.23 (br s, 6H).

^{13}C NMR (DMSO-d_6)δ; 174.2 (C), 155.4 (C), 77.1 (C), 39.6 (CH_2), 33.5 (CH_2), 29.3 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 28.1 (CH/CH_3) 26.0 (CH_2), 24.3 (CH_2).

Anal. Calc. for $C_{13}H_{25}NO_4$; C, 60.20; H, 9.72; N, 5.40. Found: C, 60.30; H, 9.66; N, 5.33.

Example 4: (N-*tert*-Butoxycarbonylphenylalanyl)-8-aminocaprylic acid (5).

To a 250 mL round bottom flask equipped with an addition funnel was added a solution of sodium 8-aminocaprylate (14.61 mmol, 32.5 mL, 1.2 equiv). The pH of the solution was adjusted to 8.2 by addition of concentrated HCl. The solution was cooled in an ice-bath. Boc-Phe-OSu (12.42 mmol, 4.50 g, 1.0 equiv) was dissolved in 1,4-dioxane (20 mL) and added dropwise. The mixture was stirred in the ice-bath for 30 min and at ambient temperature for 12 h. The solution was acidified with 1 M sulfuric acid (80 mL) and extracted with ether (100 + 50 mL). The combined organic layers were washed with water (40 mL), dried and evaporated to give a pale yellow oil. The oil was triturated with hexanes (3 x 50 mL) to afford (*N-tert*-butoxycarbonylphenylalanyl)-8-aminocaprylic acid (5) (2.17 g, 43%) as a colorless solid.

Properties are listed below.

Mp 96-100°C.

IR (Kbr): 3296, 2980, 1705, 1677, 1631, 1558, 1407 cm^{-1}.

^{1}H NMR (DMSO-d_6)δ; 12.00 (br s, 1H), 7.82 (t, J=5.34 Hz, 1H), 7.18 (m, 5H, 6.86 (d,J=8.58 Hz, 1H), 4.09 (M, 1H), 3.00 (m, 2H), 2.88 (dd, J=5.09, 13.64 Hz, 1H), 2.72 (dd,J=9.72, 13.51 Hz, 1H), 2.17 (t,J=7.31 Hz, 2H), 1.47 (m,2H), 1.29 (2 overlapped br s, 19H).

^{13}CNMR (DMSO-d_6)δ; 174.2 (C), 171.0 (C), 137.9 (CH/CH_3), 129.0 (CH/CH_3), 127.8 (CH/CH_3), 125.9 (CH/CH_3), 77.8 (C), 55.54 (CH/CH_3), 38.3 (CH_2), 37.7 (CH_2), 33.5 (CH_2), 28.8 (CH_2), 28.3 (2 x CH_2), 27.9 (CH/CH_3), 26.0 (CH_2), 24.3 (CH_2).

MS (FAB, thioglycerol): 407 (13,M^{+1} + 1), 351 (13), 307 (100), 289 (5), 261 (11). HRMS (EI) calc. for $C_{22}H_{35}N_2O_5$ (M^{+1} + 1) 407.2546, found 407.2562; calc. for $C_{22}H_{34}N_2O_5$ (M^{+1}) 406.2468, found 406.2476.

Anal. Calc. for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, 64.43; H, 8.24; N, 6.73.

Example 5: Synthesis of 2-Azacyclohexanone.

Following the procedure of Example 1 and substituting cyclopentanone for cyclooctanone, 2-azacyclohexanone is prepared.

Example 6: Sodium 6-aminopentanoate.

Following the procedure of Example 2 and substituting 2-aza-cyclohexanone for 2-azacyclononanone, sodium 6-aminopentanoate is prepared.

Example 7: 6-(*tert*-Butoxycarbonylamino)pentanoic acid.

Following the procedure of Example 3 and substituting sodium 6-aminopentanoate for sodium 8-aminocaprylate, 6-(*tert*-butoxycarbonyl-amino)pentanoic acid is prepared.

Example 8: (N-*tert*-Butoxycarbonylphenylalanyl)-6-aminopentanoic acid.

Following the procedure of Example 4 and substituting sodium 6-aminopentanoate for sodium 8-aminocaprylate, (N-*tert*-butoxycarbonyl-phenylalanyl)-6-aminopentanoic acid is prepared.

Example 9: (N-*tert*-Butoxycarbonyl-Phe-Phe)-6-aminopentanoic acid.

Following the procedure of Example 4 and substituting sodium 6-aminopentanoate for sodium 8-aminocaprylate and Boc-Phe-Phe-OSu for Boc-Phe-OSu, (N-*tert*-butoxycarbonyl-Phe-Phe)-6-aminopentanoic acid is prepared.

Example 9: (N-*tert*-Butoxycarbonyl-Phe-Phe)-6-aminopentanoic acid.

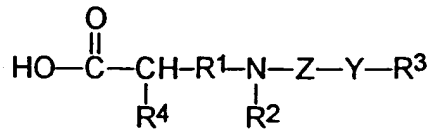
Following the procedure of Example 4, substituting sodium 6-aminopentanoate for sodium 8-aminocaprylate and Boc-Phe-Phe-OSu for Boc-Phe-OSu, (N-*tert*-butoxycarbonyl-Phe-Phe)-6-aminopentanoic acid is prepared.

The above mentioned patents, applications, test methods, and publications are hereby incorporated by reference in their entirety.

Many variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the full intended scope of the appended claims.

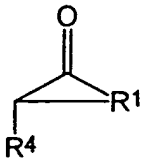
WHAT IS CLAIMED IS:

1. A method for preparing a compound having the formula

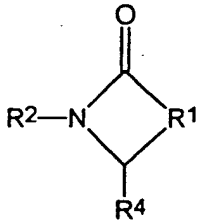


said method comprising:

(a) reacting a cycloalkanone compound having the formula:



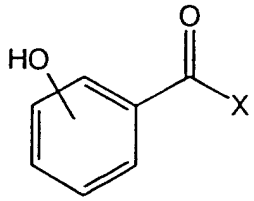
with an hydroxylamine-*O*-sulfonic acid to provide a lactam having the formula:



(b) reacting said lactam with an aqueous base to form an amine salt; and

(c) acylating said amine salt with a compound having the formula:

$(CH_3)_3C - O - CO - Z - X$; or



or a Boc protected amino acid succinate ester;

wherein

Y is carbonyl or oxycarbonyl;

Z is a bond or an amino acid residue;

R^1 is C_5-C_9 alkyl;

R^2 is hydrogen;

R^3 is *tert*-butyl or hydroxyphenyl;

R^4 is hydrogen; and

X is a leaving group.

2. The method according to claim 1, wherein the amine salt is acylated with a compound having the formula $(CH_3)_3C–O–CO–X$, wherein X is a halide.

3. The method according to claim 1, wherein the amine salt is acylated with a compound having the formula $((CH_3)_3C–O–CO)_2O$.

4. The method according to claim 1, wherein the amine salt is acylated with a Boc protected amino acid succinate ester.

5. The method according to claim 4, wherein the amine salt is acylated with Boc-phenyl alanyl-O-succinate ester.

6. The method according to claim 4, wherein the amine salt is acylated with Boc-phenyl alanyl-phenyl alanyl-O-succinate ester.

7. The method according to claim 1, wherein R1 is alkyl having 6 carbon atoms, Z is a bond, Y is carbonyl, and R^3 is 2-hydroxyphenyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/14805

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 51/10, 51/14, 227/00; C07B 43/00
US CL :562/517; 554/114
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 562/517; 554/114

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,933,873 A (LOVE ET AL.) 20 January 1976, entire document.	1-7
A	US 3,816,404 A (KABLAOUI ET AL.) 11 June 1974, entire document.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 DECEMBER 1996

Date of mailing of the international search report

23 JAN 1997

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